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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,433	10/12/1999	DAVID SIDRANSKY	JHU1180-1	2810

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/420,433	SIDRANSKY, DAVID	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-14,18-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-14,18-22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 10, 2003 has been entered.

2. The current status of the claims is as follows: claims 5-6, 15-17, 23, and 27 are canceled, and claims 1-4, 7-14, 18-22, and 24-26 are now pending and under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 7-14, 18-22, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1-7 and 7-11 are drawn to methods in which a "mutant target nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a tumor margin tissue specimen that is "external to a primary neoplasm" and which "does not exhibit morphological characteristics indicative of neoplastic pathology." Claims 12-14 are drawn to methods in which a "neoplastic nucleic acid having a mutant nucleotide sequence" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a surgical margin by oligonucleotide hybridization. Claim 18 encompasses detection of such a neoplastic nucleic acid in a "tissue specimen which is external to a primary neoplasm," while claim 19 requires the presence of such a sequence in a "tumor margin tissue specimen." Claims 20-22 and 24 are drawn to methods in which a "mutant target nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a "lymph node tissue specimen" that is "external to a primary neoplasm" and which "does not exhibit morphological characteristics indicative of neoplastic pathology." Claims 25-26 are drawn to methods in which a "neoplastic nucleic acid having a mutant nucleotide sequence" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected

in lymph node tissue by oligonucleotide hybridization, wherein the lymph node is "external to a primary neoplasm" and "does not exhibit morphological characteristics indicative of neoplastic pathology."

It is unpredictable as to whether one of skill in the relevant art could use the invention of the instant claims. The specification asserts that each of the "neoplastic" or "mutant" nucleic acids recited in the instant claims may be detected in tumor margins and lymph node tissues that do not "exhibit morphological characteristics indicative of neoplastic pathology." However, the specification only exemplifies the detection of a different mutated nucleic acid, p53, in surgical margins and lymph nodes that appear histologically normal in patients afflicted with head and neck squamous cell carcinoma (see Examples 1-4, as well as Figures 2-5 and 7-9). The specification does not provide any evidence that mutated versions of any of the nucleic acids recited in the instant claims can actually be detected in histologically normal surgical margins or lymph nodes in patients with any type of cancer. Lacking guidance from the specification, one of skill in the art may looking to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art is also silent with respect to any teachings that mutant versions of any of the genes of the instant claims may be detected in histologically normal surgical margins or lymph nodes. The prior art does support Applicant's findings with respect to detection of p53 in histologically normal tissues. For example, Deguchi et al (Cancer Research 53:5350-5354 [11/1993]) disclose that p53 mutations were detected in histologically normal lymph nodes from prostate cancer patients (see, e.g., Table 1 and page 5353), and Nees et al (Cancer

Research 53(18):4189-4196 [9/1993]) disclose that mutated p53 nucleic acids were detected in tumor margin specimens obtained from patients with head and neck cancers (see, e.g., Table 3, p. 4191, 4193). Nees et al further teach that their finding of p53 mutations in histological normal tissue adjacent to a tumor indicates that mutation of p53 is likely an early event in head and neck carcinogenesis (see page 4189, right column)(i.e., the mutations occurs sufficiently early that they are present before histological evidence of cancer is present). Thus, the teachings of the art suggest that only "neoplastic nucleic acids" that are mutated early in the process of carcinogenesis associated with a particular type of cancer would be detectable prior to the development of histological evidence of that cancer. Accordingly, absent actual evidence that a particular mutation or mutations in a particular nucleic acid occur sufficiently early in the development of cancer so as to be detectable prior to histological changes in lymph nodes and/or surgical margins, one skilled in the art would not expect to be able to accomplish such detection. Neither the specification nor the art provide evidence that any of the nucleic acids of the claims are mutated at a sufficiently early point in the development of any type of cancer so as to be evident prior to the detection of morphological changes associated with cancer. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct further experimentation aimed at determining whether any of the particular nucleic acids of the instant claims are actually mutated at a sufficiently early point in time such that mutations are detectable prior to the occurrence of any histological changes in tumor margins and/or lymph nodes. However, as the outcome of such experimentation cannot

be predicted, it is unknown as to whether any quantity of experimentation would actually be sufficient to enable the practice of the claimed invention. Accordingly, it would clearly require undue experimentation to use the invention of the instant claims.

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Patent Examiner
March 22, 2004